Collaborative overview of randomised trials of antiplatelet therapy—III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients

Antiplatelet Trialists' Collaboration

This is the concluding part of the overview of randomised trials of antiplatelet therapy. Part II, on maintaining vessel patency, was published last week.

Abstract

***Objective*—To determine the efficacy of antiplatelet therapy as prophylaxis against deep venous thrombosis or pulmonary embolism in surgical and high risk medical patients.**

***Design*—Overviews of all randomised trials of antiplatelet therapy that could have been available by March 1990 and in which deep venous thrombosis was assessed systematically.**

***Setting*—53 trials (total 8400 patients) of an average of two weeks of antiplatelet therapy versus control in general or orthopaedic surgery; nine trials (600 patients) of antiplatelet therapy versus control in other types of immobility; 18 trials (1000 patients) of one antiplatelet regimen versus another.**

***Results*—Overall, a few weeks of antiplatelet therapy produced a highly significant ($2P < 0{\cdot}00001$) reduction in deep venous thrombosis. 25% of patients allocated antiplatelet therapy versus 34% of appropriately adjusted controls had deep venous thrombosis detected by systematic fibrinogen scanning or venography, representing prevention in about 90 patients per 1000 allocated antiplatelet therapy. There was an even greater proportional reduction in pulmonary embolism: such emboli were detected among 47 (1·0%) antiplatelet allocated patients versus an adjusted control total of 129 (2·7%), representing prevention among about 17 patients per 1000 treated ($2P < 0{\cdot}00001$). In analyses confined to surgical trials, the proportional reductions were similar and separately significant for non-fatal pulmonary embolism (0·7% antiplatelet therapy *v* 1·8% control; $2P < 0{\cdot}00001$) and for deaths attributed to pulmonary embolism (0·2% *v* 0·9%; $2P = 0{\cdot}0001$). There was a slight but non-significant excess of deaths from other causes (1·0% *v* 0·7%), which made the difference in total mortality non-significant, though still favourable (1·2% *v* 1·5%). Information on adding antiplatelet therapy to heparin was limited but, at least for pulmonary embolism, suggested more protection from the combination than from heparin alone.**

The proportional reduction in the odds of suffering a deep venous thrombosis was roughly the same in patients having general surgery, traumatic orthopaedic surgery, and elective orthopaedic surgery (and in medical patients who were at increased risk of thromboembolism). For pulmonary embolism the numbers affected were smaller, but again the reductions were highly significant both in general surgery (16 (0·5%) *v* 58 (1·7%) pulmonary emboli; $2P < 0{\cdot}0001$) and in orthopaedic surgery (28 (2·7%) *v* 63 (6·1%) pulmonary emboli; $2P < 0{\cdot}0002$).

***Conclusion*—It had previously been supposed that antiplatelet therapy did not influence venous thromboembolism, and many surgeons and physicians do not use it routinely for thromboprophylaxis, even for patients who are at substantial risk of deep venous thrombosis or pulmonary embolism. These results indicate that antiplatelet therapy—either alone or, for greater effect, in addition to other proved forms of thromboprophylaxis (such as subcutaneous heparin)—should be considered.**

Antiplatelet Trialists' Collaboration
A full list of collaborators was given at the end of part I, published on 8 January.

Correspondence to:
APT Statistical Secretariat, ICRF/BHF/MRC Clinical Trial Service Unit, Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford OX2 6HE, or APT Clinical Secretariat, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU.

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Introduction

During prolonged general anaesthesia or any other period of limited mobility thrombus formation may be initiated in the deep veins of the legs. Specific tests disclose deep venous thrombosis in about a quarter of all patients who have had general surgery and in about half of those who have had orthopaedic surgery.[1] Most such thromboses are subclinical and resolve completely when mobility is restored (though a few produce permanent valvular damage and chronic venous insufficiency), but some may embolise to the lungs, producing slight, substantial, or fatal effects.

Venous thrombosis and pulmonary embolism remain an important cause of morbidity and mortality both in surgical patients and in immobilised medical patients.[2-4] Various thromboprophylactic treatments have therefore been devised to prevent or limit thromboembolism.[3-10] An overview of randomised trials of perioperative subcutaneous heparin[10] showed that among surgical patients such treatment can roughly halve the risk not only of deep venous thrombosis but, more importantly, of pulmonary embolism. Subcutaneous heparin is now widely recommended for surgical or medical patients at high risk of venous occlusion, but antiplatelet therapy still is not.[3-8] This report provides an overview of the results of the randomised trials of antiplatelet therapy in which deep venous thrombosis was to be assessed systematically. Most such trials entailed a few weeks of perioperative treatment in general or orthopaedic surgery, but some entailed a few months of treatment for long stay medical patients at high risk of venous thromboembolism (for example, those immobilised by a stroke or myocardial infarction or who suffer recurrent venous thrombosis).

NUMBERS NEEDED TO ASSESS EFFICACY RELIABLY

Antiplatelet therapy has been shown in various settings to reduce the risk of myocardial infarction, cerebral infarction, and other arterial occlusion (see parts I and II[11,12]). This report reviews its effects on venous occlusion and pulmonary embolism. Antiplatelet therapy has previously not generally been accepted to prevent deep venous thrombosis or pulmonary embolism,[3-8] but this may be because the trials had been too small to be separately convincing.

Most randomised trials of the thromboprophylactic effects of anticoagulant or antiplatelet therapy have been conducted in patients undergoing surgical procedures. Antiplatelet trials including about 1000 general surgical patients or about 400 of the higher risk orthopaedic surgical patients might be required for reliable detection of a reduction of about 40% in the occurrence of deep venous thrombosis (that is, an effect similar in size to that seen with the most widely

used pharmacological prophylactic measure, subcutaneous heparin[10]; table I). To date, however, the largest trial of the effect of antiplatelet therapy on deep venous thrombosis after general surgery has included only a few hundred patients, while the largest in orthopaedic surgery included fewer than 300 relatively low risk patients.[13-78] The lack of any clearly significant reductions in deep venous thrombosis in most previous trials may therefore reflect lack of statistical power rather than lack of therapeutic efficacy.

The situation is still worse for directly randomised assessment of any effects of antiplatelet therapy on pulmonary embolism, as detectable emboli typically occur among only a few per cent of the control patients in these surgical trials. Trials in more than 10 000 "typical risk" general surgical patients or 4000 "high risk" orthopaedic surgical patients might therefore be required to be able to detect reliably a 40% reduction in the probability of suffering pulmonary embolism (table I).

NEED FOR A SYSTEMATIC OVERVIEW OF TRIALS

Prophylaxis with a simple antiplatelet regimen would be widely practicable to administer, even (in contrast with many other forms of prophylaxis) during the period after discharge from hospital while the risk of thromboembolism may still be raised.[79 80] Hence if antiplatelet therapy does produce a worthwhile prophylactic effect it is important not to overlook this by considering the results of just a few individual trials taken in isolation from the rest of the trial evidence. To help avoid any such false negative results, assessment of the thromboprophylactic effects of antiplatelet therapy should be based on a systematic overview of the evidence from all relevant randomised trials. This will reduce the effects of the play of chance on the overall results and also help to avoid the selection biases that might arise from undue emphasis being placed on the results of just one, or only a few, of the relevant trials.[81] The aim of this overview of antiplatelet trial results is to assess as reliably as possible whether such treatment prevents deep venous thrombosis and, particularly, pulmonary embolism or death from pulmonary embolism (and, if so, whether the proportional reductions are similar in different types of surgery). Wherever possible information on any serious bleeding complications was also reviewed.

Materials and methods

DATA ACQUISITION

Identification of all unconfounded randomised trials

The aim was to include all unconfounded randomised trials of antiplatelet therapy versus no antiplatelet therapy, or of one antiplatelet regimen versus another, that could have been available for review by March 1990 and in which deep venous thrombosis was systematically monitored by any method (see below and appendices 1 and 2). A fuller description of the methods used for seeking trials and data was given in part 1.[11] Relevant randomised trials were identified in general surgery (29 trials; 6691 patients[13-40]), in traumatic orthopaedic surgery (11 trials; 964 patients[41-48]), in elective orthopaedic surgery (18 trials; 1154 patients [49-67]), and among high risk medical patients (11 trials; 814 patients[68-78]).

As in part I, trials were to be excluded if allocation was believed not to have been randomised in a manner that precluded prior knowledge of the next treatment (for example, where allocation was alternate or based on odd or even dates or record numbers, or where the comparison was to be with some historical controls) or if the treatment comparisons were considered to be confounded (that is, where the scheduled treatment in one group differed from that in the other in some aspect other than antiplatelet therapy). Hence randomised comparisons of antiplatelet therapy versus heparin or versus other potential thromboprophylactic measures were not to be included, though trials of antiplatelet plus anticoagulant regimens versus the same anticoagulant regimen alone were to be. Trials that were not available for review by March 1990, generally because they were still in progress (see references in part I), do not contribute to the main analyses.

Principal analyses and outcome measures

The principal analyses of the effects of antiplatelet therapy on deep venous thrombosis were to be based on the results of only those randomised trials in which such thromboses were sought prospectively by systematic venography or systematic radiolabelled fibrinogen uptake tests (with or without confirmatory venography), or both. The principal analyses of the effects on pulmonary embolism, however, were to be based on all trials that sought venous thrombosis prospectively, irrespective of the method used, as in all such trials the interest in venous thrombosis would tend to ensure that any pulmonary emboli diagnosed would be recorded. (Restriction to the trials where venous thrombosis was to be assessed should help to minimise any potential for biases due to selective reporting in other trials, where pulmonary emboli might be reported only if their relation with treatment seemed "noteworthy"; nevertheless, some analyses of the numbers of pulmonary emboli in those other trials[11 12] will be provided alongside the principal analyses.)

Information was sought on deep venous thrombosis, pulmonary embolism, and mortality (distinguishing between deaths ascribed to pulmonary embolism, bleeding, and all other causes). Information was also sought on any haemorrhage that was either fatal or severe enough to require transfusion (here defined as a "major" bleed). Other measures of perioperative haemorrhagic complications (such as bleeds resulting in reoperation, wound haematomas, or infection) were also sought, but the definitions used were not uniform and such measures were not available for many trials.

When the data collected did not include information about outcome among all patients initially randomly assigned on all of the outcomes of interest extra details were sought from the principal investigators (see part I). In trials in which some patients had been excluded after randomisation from the published report it was often possible to obtain by correspondence follow up information on these outcome measures among most or all of the missing patients so that appropriately unbiased intention to treat analyses of such events could be conducted. When this was not possible the available data have still been included in the overview unless the number of exclusions was so extensive[82] that the trial could no longer be considered properly randomised. Analyses confined to placebo controlled studies, which may be less subject to treatment dependent biases in the assessment of subjective

TABLE I—*Numbers required for statistically reliable trials if treatment reduced risk of adverse outcome by about 40%*

Outcome measure	Typical risk patients (as in general surgery)		High risk patients (as in orthopaedic surgery)	
	Difference to be detected†	No of patients needed‡	Difference to be detected†	No of patients needed‡
Deep venous thrombosis	20%→12%	1 000	40%→24%	400
Pulmonary embolism	2·0%→1·2%	10 000	6·0%→3·6%	4 000
Death due to pulmonary embolism	0·5%→0·3%	50 000	2·0%→1·2%	10 000
Total mortality	1·0%→0·8%	100 000	3·0%→2·2%	20 000

†Consequences of 40% reduction in thrombosis (given typical control risks).
‡Total numbers needed for trials to have about 80% chance of achieving $2P < 0{\cdot}01$.

outcome measures, were also considered separately, when appropriate.

STATISTICAL METHODS

Proportional and absolute reductions

Statistical methods used to obtain an overview of the results from the trials were detailed in part I. Proportional reductions in venous occlusion or emboli may be more widely generalisable to somewhat different medical circumstances, whereas absolute reductions may be more directly relevant to deciding whether to use therapy in particular medical circumstances. Standard methods for combining trial results[11 83-85] that provide an unbiased test of whether treatment has any effect at all can also provide an estimate of the "typical" proportional reduction in the odds of adverse events observed in the trials. (These methods are completely robust and do not assume that the real proportional effects of treatment are all exactly the same in the different trials but assume merely that any real effects probably point in the same direction. Fuller discussion has been given elsewhere.[85]

When the overall difference between treatment and control patients is very highly significant and all the trials are approximately evenly randomised, a simple description of the absolute reduction can be provided just by adding together all the treatment groups, adding together all the control groups, and comparing these two grand totals. (If any of the trials include deliberately uneven treatment allocation—for example, two thirds treatment versus one third control—then it can first be "adjusted" to an evenly randomised comparison by counting the control group more than once; see part I.)

Even when there is a highly significant overall effect, separate analyses of the effects in small subgroups of patients may be statistically unstable. Consequently, unless there are good prior reasons for expecting large differences between the effects of treatment in different circumstances, the approximate benefit of antiplatelet therapy in some particular subgroup may best be assessed indirectly, not from an analysis that is restricted just to that one subgroup but, instead, by approximate extrapolation from the proportional effect that is observed in a much wider class of patients[86] (see discussion in part I).

Results

EFFECTS OF ANTIPLATELET THERAPY ON DEEP VENOUS THROMBOSIS

Information on deep venous thromboses detected by systematic venography or systemic fibrinogen scanning (with any confirmatory phlebography), or both, was available for 45 trials of antiplatelet therapy among surgical patients and for eight such trials among high risk medical patients. The proportional odds reductions are shown in figure 1 and (of more direct relevance to medical practice) the absolute reductions in risk are shown in figure 2.

Proportional benefits

The total numbers of patients suffering a deep venous thrombosis among those allocated antiplatelet

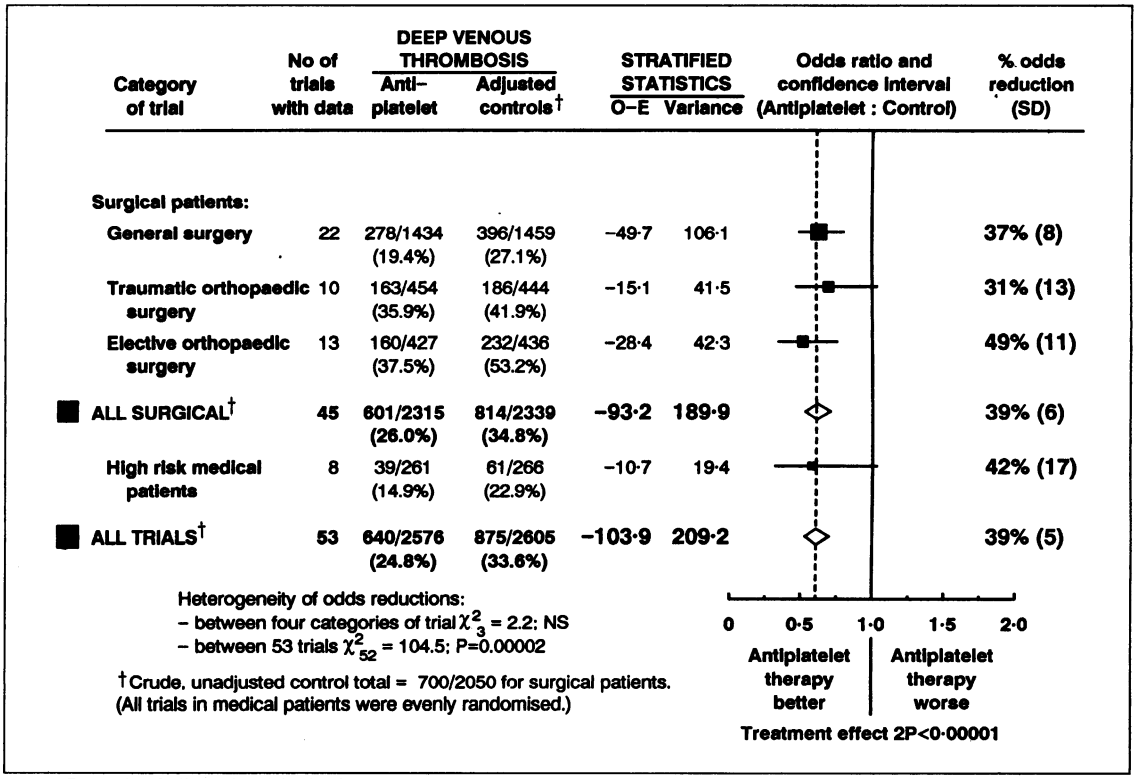

FIG 1—*Proportional effects of antiplatelet therapy on numbers of patients in whom deep venous thrombosis was detected by systematic fibrinogen scans or venography, or both, after general and orthopaedic (traumatic and elective) surgery and in high risk medical patients. O–E=Observed minus expected*

(In most trials patients were allocated roughly evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparisons between percentages observed to have an event in each treatment group, adjusted totals have been calculated after converting any unevenly randomised trials to even ones by counting control groups more than once. Statistical calculations are, however, based on actual numbers from individual trials and crude, unadjusted control totals are given. Stratified ratio of odds of deep venous thrombosis in treatment group to that in control group is plotted for each group of trials (black square: area proportional to amount of information contributed) along with its 99% confidence interval (horizontal line). Black square to left of solid vertical line suggests benefit (significant at 2P<0·01 only where entire confidence interval is to left of solid vertical line). Overviews of results for certain subtotals of trials (and 95% confidence intervals) are represented by diamonds. Observed reductions in odds of deep venous thrombosis in particular groups of trials are given to right of solid vertical line)

Risk reduction and odds reduction: Crude totals with deep venous thrombosis (25% and 34%) suggest risk reduction of about one quarter but odds reduction of about one third. These crude risks are equivalent to odds of 25/75 (0·33) and 34/64 (0·53) respectively (indicating odds ratio of about 0·33/0·53 (=0·63)—that is, approximate odds reduction of about 37%, which is similar to result (39% (SD 5%)) of more formal statistical analysis)

therapy were 640/2576 (24·8%), while the corresponding adjusted total among controls was 875/2605 (33·6%). These crude risks of 25% and 34% indicate a risk reduction of about one quarter, which corresponds to an odds reduction of somewhat more than one quarter (see legend to figure 1). More formal statistical methods for combining the results from these 53 trials, which entail no unjustified assumptions,[11] indicate that the typical reduction in the odds of suffering deep venous thrombosis was about 39% (with standard deviation (SD) 5%), which is very highly significantly favourable ($2P<0·00001$; fig 1). In principle it is possible that some of these results might have been somewhat biased by knowledge (when assessing deep venous thrombosis) of which patients had been allocated antiplatelet therapy and which had been allocated control. In practice, however, this seems to have made little difference, for when the analyses were confined to those trials in which the controls were given a placebo the odds reduction became 38% (SD 7%), which is just as large as before and still highly significant ($2P<0·00001$).

Most of the trials concerned patients having surgery, among whom the mean duration of antiplatelet therapy was only two weeks. The proportional reductions were similar and highly significant in each main category of surgery—general surgery (37% (SD 8%) proportional reduction; $2P<0·00001$), traumatic orthopaedic surgery (31% (SD 13%) reduction; $2P=0·02$), and elective orthopaedic surgery (49% (SD 11%) reduction; $2P<0·0001$; fig 1). Even among the few high risk medical patients, among whom the mean duration of antiplatelet therapy was to be eight weeks, there appeared to be a substantial proportional reduction (42% (SD 17%); $2P=0·02$) in the odds of having detectable thrombus. There was no significant difference between the odds reductions observed in each of the four main categories of trial, but there were significant differences between the effects observed in the 53 separate trials (see foot of fig 1). This heterogeneity of the size of the reduction in deep venous thrombosis was largely confined to trials in general surgery (heterogeneity: $\chi^2=57·2$, $df=21$; $P<0·0001$), a category which may include a much greater range of different types and durations of surgery (and, hence, of thromboembolic risk) than did orthopaedic surgery, which was largely confined to hip operations.

Absolute benefits

It is not the proportional but the absolute reductions that determine how worth while therapy is, and as the proportional reductions in different types of patient appeared similar (fig 1), the absolute reductions appeared to be greatest among patients at highest risk of a deep venous thrombosis (fig 2). For example, in patients having elective orthopaedic surgery allocation to a mean scheduled duration of two weeks of antiplatelet therapy was associated with prevention of deep venous thrombosis in 157 (SD 33) patients per 1000 (37·5% of antiplatelet allocated patients versus 53·2% of corresponding controls), and in those having traumatic orthopaedic surgery allocation to a mean of two weeks of antiplatelet therapy prevented thromboses in 60 (SD 29) patients per 1000 (35·9% antiplatelet therapy *v* 41·9% control). Even among the lower risk general surgical patients, however, the absolute benefits remained substantial, with allocation to a mean of only one week of antiplatelet therapy preventing thromboses in 78 (SD 18) patients per 1000 (19·4% antiplatelet therapy *v* 27·1% control). Thrombi in the proximal (femoral and iliac) veins of the leg are particularly likely to embolise to the lungs, and in the 14 of these trials for which information on proximal thromboses was separately available, antiplatelet therapy was associated with a 52% (SD

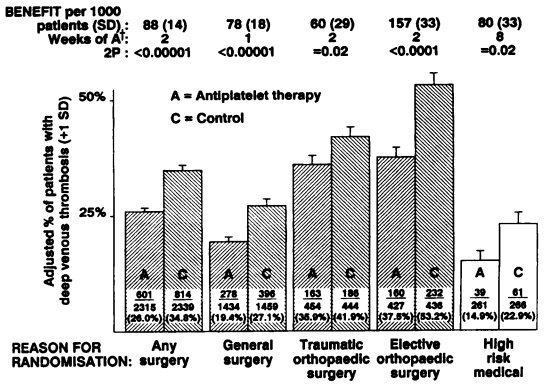

FIG 2—*Absolute effects of antiplatelet therapy on deep venous thrombosis detected by systematic fibrinogen scans or venography, or both, after general and orthopaedic (traumatic and elective) surgery and in high risk medical patients*

(Adjusted totals calculated after converting any unevenly randomised trials to even ones by counting control groups more than once, for calculating adjusted percentages and numbers of patients prevented from having deep venous thrombosis per 1000 allocated antiplatelet therapy. Numbers of high risk medical patients studied are small, so these results are denoted by open bars. (Significance (2P) based on stratified analyses of original, unadjusted numbers in each trial; see statistical methods in part I[11])

†Weeks of A = Means of scheduled antiplatelet durations.

12%) reduction in the odds of a proximal thrombus developing ($2P=0·00002$).

Fibrinogen leg scanning may be rather insensitive to the femoral and iliac vein thromboses that commonly occur after orthopaedic surgery, and is also prone to giving false positive results because of extravasation of radiolabelled fibrinogen at the site of any internal bleeding.[87 88] Such deficiencies might weaken the estimated effects of treatment but they should not produce falsely positive evidence of protection. For, if treatment had no effect, then these limitations would apply at least as much to patients assigned antiplatelet therapy as to controls; indeed, as antiplatelet therapy might somewhat increase such bleeding, false positive results due to extravasation might, if anything, be increased by treatment. Hence the significant decrease in thrombosis that was detected by radiolabelled fibrinogen scanning provides valid evidence of benefit, which is reinforced by analyses of the thrombi that were confirmed by venography (49% (SD 10%) reduction in the 15 trials that provided such data; $2P<0·00001$).

In principle, possibly the decision to perform venography might have been influenced in some of these studies by an interpretation of the fibrinogen scan that was biased by knowledge of the treatment allocation. Even in the placebo controlled studies, however, there was a similar sized reduction in patients with venographically confirmed thrombi (44% (SD 11%); $2P=0·00006$). Moreover, a few small randomised trials of antiplatelet therapy included systematic venography (which would not be subject to such ascertainment bias), and though the numbers of patients with deep venous thromboses detected were small, a significant 69% (SD 23%) reduction was still observed (adjusted totals: 9 (11%) of 85 allocated antiplatelet therapy *v* 25 (29%) of 85 allocated control in three trials; $2P=0·002$). Hence assessment biases can account for little, if any, of the protective effect shown.

EFFECTS OF ANTIPLATELET THERAPY ON PULMONARY EMBOLISM

Information on pulmonary embolism was available from 62 of the 64 trials in which deep venous thrombosis had been sought systematically (by fibrinogen scanning or venography (the 53 trials in figures 1 and 2), or by other methods (11 additional

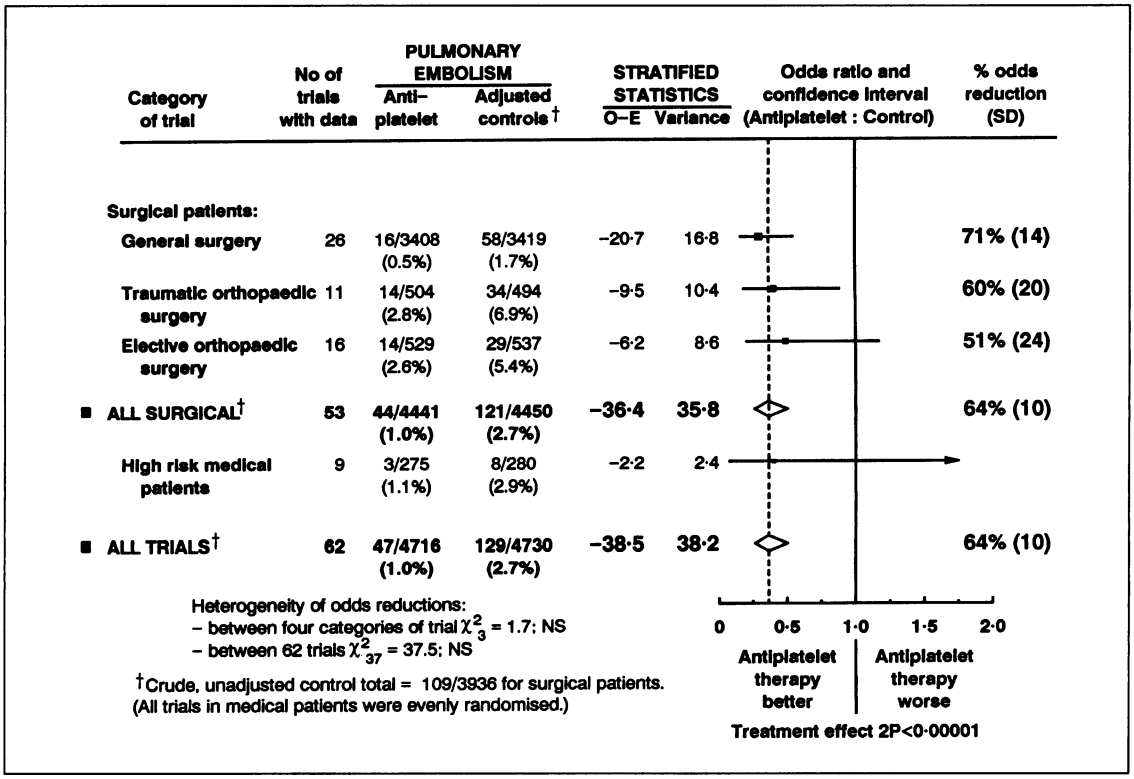

FIG 3—*Proportional effects of antiplatelet therapy on numbers of patients observed to have pulmonary embolism in trials that sought venous thrombosis systematically after general and orthopaedic (traumatic and elective) surgery and in high risk medical patients. Symbols and conventions as in figure 1*

trials; see appendices 1 and 2)). Pulmonary emboli were observed among only 47 (1·0%) of the 4716 patients allocated antiplatelet therapy compared with an adjusted control total of 129/4730 (2·7%). This threefold difference was highly significant ($2P < 0·00001$; fig 3) and represented a 64% (SD 10%) reduction in the odds of suffering a pulmonary embolism. (A similar sized reduction (56% (SD 14%); $2P < 0·0001$) in pulmonary embolism remained when just the 53 trials from figures 1 and 2 were considered.) Pulmonary emboli were usually diagnosed clinically, with confirmation by ventilation-perfusion scanning or necropsy, or both. In principle, ascertainment of pulmonary embolism might have been influenced by knowledge of the allocated treatment group, but in practice the results remained much the same when the analyses were confined to placebo controlled trials (65% (SD 11%) reduction; $2P < 0·00001$).

As in the case of deep venous thrombosis, separately significant and similar sized proportional reductions in pulmonary embolism were seen in each main category of surgery—general surgery (71% (SD 14%) proportional reduction; $2P < 0·00001$), traumatic orthopaedic surgery (60% (SD 20%); $2P < 0·005$), and elective orthopaedic surgery (51% (SD 24%); $2P = 0·04$; (fig 3). The absolute benefits again therefore appeared to be greater in the higher risk patients (fig 4). For example, just a few weeks of antiplatelet therapy after elective orthopaedic surgery was associated with prevention of pulmonary embolism in 28 (SD 12) patients per 1000 (2·6% of antiplatelet allocated patients versus 5·4% of corresponding controls) and after traumatic orthopaedic surgery it prevented pulmonary emboli in 41 (SD 14) patients per 1000 (2·8% antiplatelet therapy *v* 6·9% control). The absolute benefit observed after general surgery was smaller, with prevention of pulmonary embolism among 12 (SD 3) patients per 1000, but still highly significant ($2P < 0·00001$). Among the few high risk medical patients the protective effect against venous thrombosis shown in figures 1 and 2 indicated some protection against pulmonary embolism as well, but although the available data support this suggestion, too few pulmonary emboli were recorded in medical patients (three antiplatelet therapy *v* eight control) for this to be tested accurately.

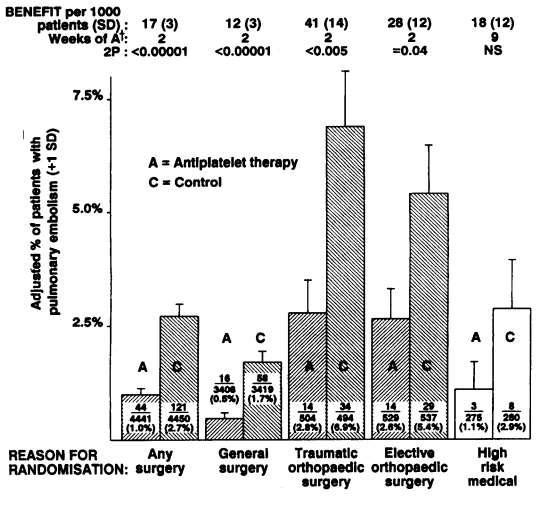

FIG 4—*Absolute effects of antiplatelet therapy on pulmonary embolism in trials that sought venous thrombosis systematically after general and orthopaedic (traumatic and elective) surgery and in high risk medical patients. Symbols and conventions as in figure 2*

†Weeks of A = Means of scheduled antiplatelet durations.

Some additional information about the effects of antiplatelet therapy on pulmonary embolism was available from trials in which prevention of venous thrombosis was not the main purpose (most of which entailed at least one month of therapy and so were reviewed in part I). The information from these trials was seriously incomplete, but it should not be biasedly incomplete, and it did not show as much protection as in figure 3. In the trials among people at high risk of other vascular events that are reviewed in part I, only 49 antiplatelet allocated patients versus an adjusted total of 54 controls had a pulmonary embolism recorded during an average of two years of follow up (0·3% of the patients from each treatment group in trials in which at least one pulmonary embolism was recorded). Similarly, in the primary prevention trials among low risk subjects, 31 antiplatelet allocated patients versus an adjusted total of 23 controls had a pulmonary embolism recorded during about five years of follow up (0·2% of each treatment group). But when

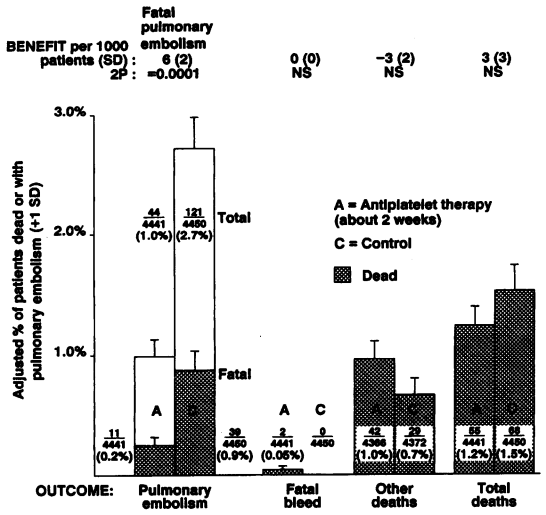

FIG 5—*Absolute effects of antiplatelet therapy on pulmonary embolism, fatal pulmonary embolism, and other deaths in 53 surgical trials that sought venous thrombosis systematically. Symbols and conventions as in figure 2*

(Figure excludes nine small trials among high risk medical patients. Denominators for other deaths are slightly smaller because one trial[17] could provide information subdivided by treatment only on fatal pulmonary emboli and bleeds and not on other deaths)

TABLE II—*Directly randomised comparisons among various types of patient of aspirin plus dipyridamole versus aspirin alone*

Category of patients and trials	Aspirin plus dipyridamole	Same aspirin	Statistics† O-E	Statistics† Variance	Significance (2P)
Patients at high risk of myocardial infarction, stroke, or vascular death:					
No with such a vascular event[11]	309/2660	312/2657	-2·4	132·6	NS
Patients at high risk of coronary or peripheral artery occlusion:					
No with such an occlusion[12]	200/951	199/950	0·6	76·9	NS
Trials that sought deep venous thrombosis by systematic fibrinogen scans or venography, or both:					
No with deep venous thrombosis‡	15/109	33/109	-9·7	8·7	=0·001
Trials with some pulmonary emboli reported:					
No with pulmonary embolism§	6/1737	5/1742	0·5	2·7	NS

†Observed minus expected (O-E) for aspirin plus dipyridamole, and variance of O-E.
‡For comparison of aspirin plus dipyridamole versus *any* aspirin dose, results were: 63/263 *v* 97/264, O-E=-16·3, variance=22·4, 2P=0·0006.
§Includes results from trials which systematically sought deep venous thrombosis of 1/297 *v* 0/304 (fig 6: in which corresponding numbers for comparison with *any* aspirin dose were 4/451 *v* 3/459) and from coronary artery bypass graft[12] trials (5/530 *v* 3/528) and other[11] trials (0/910 *v* 2/910) that found at recorded one pulmonary embolism.

these trials were considered together with the trials in figure 3 there was still a highly significant 39% (SD 9%) reduction in pulmonary embolism (127 cases among antiplatelet allocated patients versus an adjusted control total of 206; 2P=0·00003).

EFFECTS OF ANTIPLATELET THERAPY ON PERIOPERATIVE MORTALITY

The analyses of mortality in figure 5 are restricted to the 53 surgical trials in figures 3 and 4. In these the apparent effects of treatment were significant for non-fatal pulmonary embolism (33 (0·7%) non-fatal cases among 4441 antiplatelet allocated patients versus an adjusted total of 82 (1·8%) among 4450 controls; 61% (SD 13%) odds reduction; 2P<0·00001) and for deaths attributed to pulmonary embolism (11 (0·2%) fatal cases *v* 39 (0·9%); 70% (SD 18%) reduction; 2P=0·0001; fig 5). Only two deaths were attributed to haemorrhage, and both occurred among antiplatelet allocated patients. The adjusted numbers of other deaths were also greater among patients allocated antiplatelet therapy (42 (1·0%) *v* 29 (0·7%)), although this difference may merely reflect the play of chance as it was not statistically significant. But although this non-significant excess of other deaths means that total mortality was not significantly reduced, the total was still somewhat lower among patients allocated antiplatelet therapy than among the corresponding controls (fig 5). (In the nine trials among high risk medical patients, six deaths were attributed to pulmonary embolism (two antiplatelet therapy *v* four control), two were attributed to haemorrhage (nil *v* two), and there were only 44 other deaths (22 *v* 22).)

COMPARISONS OF DIFFERENT ANTIPLATELET REGIMENS

Direct comparisons between different regimens

Some direct randomised comparisons were available between the effects of aspirin and another antiplatelet regimen, or between one dose of aspirin and another, on deep venous thrombosis or pulmonary embolism, but these trials were generally too small to be reliable (fig 6). In these direct comparisons aspirin plus dipyridamole appeared to be more effective than aspirin alone at preventing deep venous thrombosis. Though this may reflect a real difference, its statistical

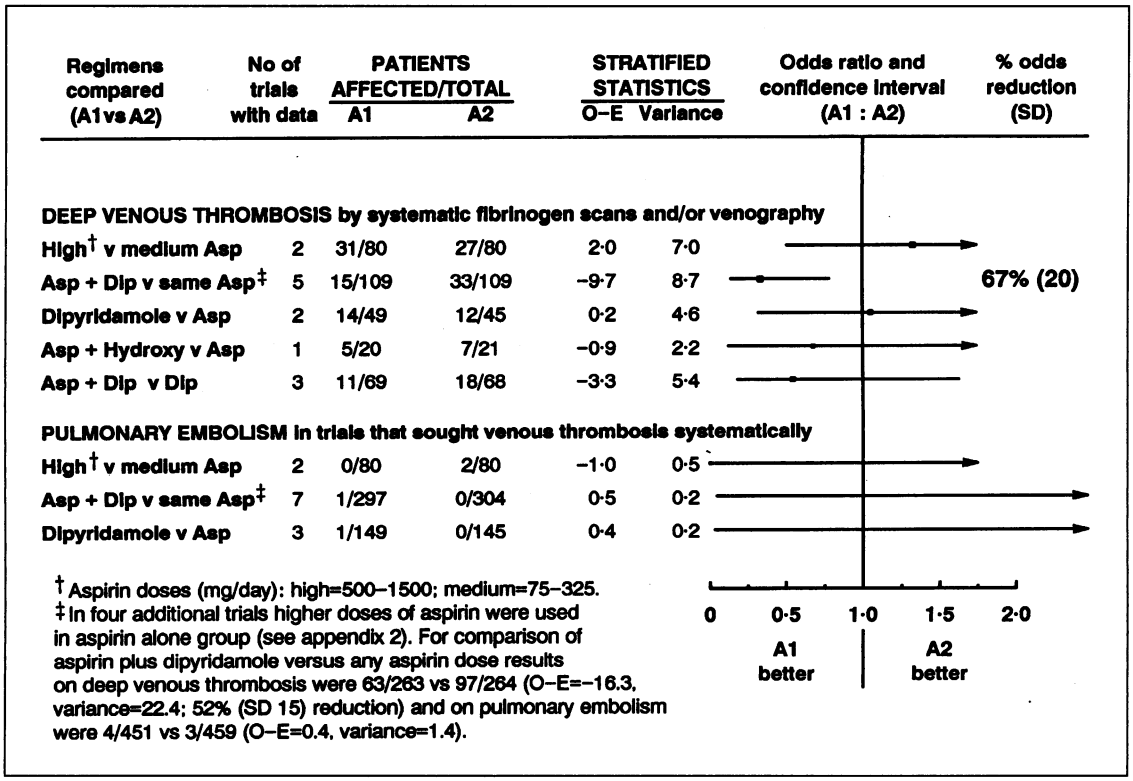

FIG 6—*Direct comparisons of proportional effects of different antiplatelet regimens on deep venous thrombosis and on pulmonary embolism. Symbols and conventions as in figure 1. Asp=Aspirin. Dip=Dipyridamole. Hydroxy=Hydroxychloroquine*

significance was not particularly striking when due account was taken (by means of a Bonferroni correction) of the many different comparisons that have been performed in all the comparisons between treatment regimens in the three parts of this overview. Moreover, the existence of a substantial additional protective effect of dipyridamole was not supported by the direct comparisons of the effects of aspirin alone versus aspirin plus dipyridamole on vascular events (part I[11]), on arterial or graft occlusion (part II[12]), or by the limited data on pulmonary embolism (fig 6; table II)

Indirect comparisons between different regimens

Figures 7 and 8 provide details of the separate effects of different antiplatelet regimens and are divided into antiplatelet therapy versus nil (that is, in the absence of

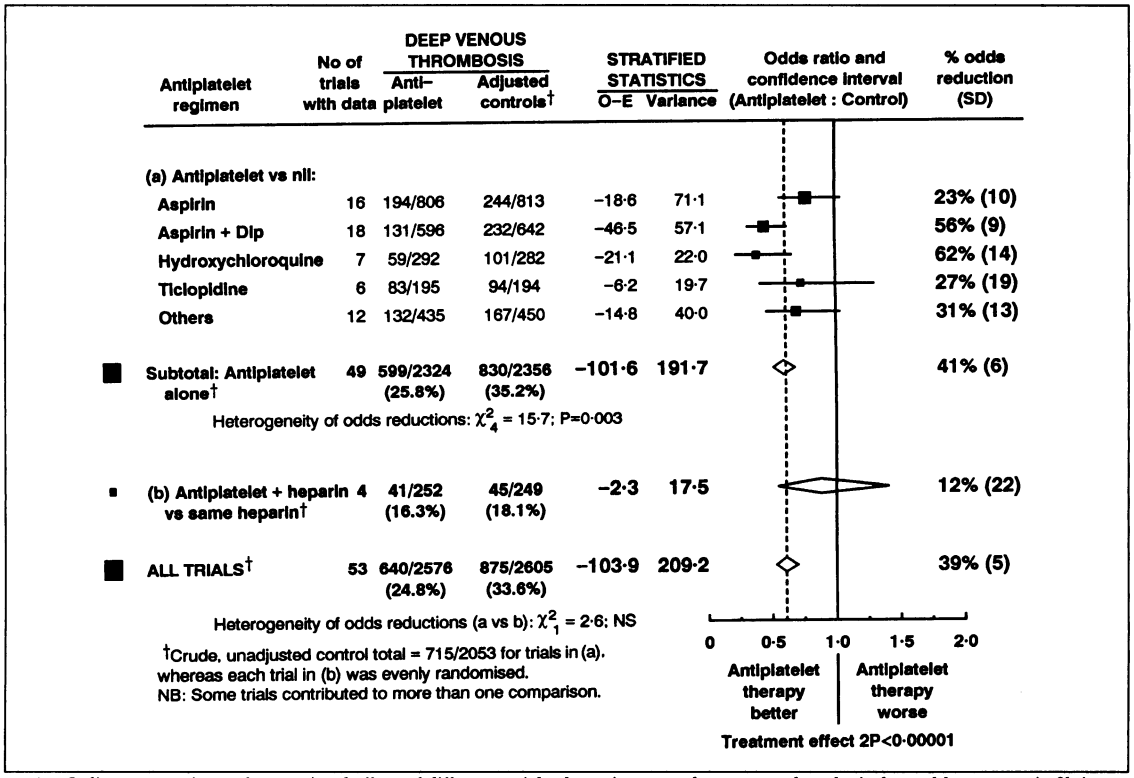

FIG 7—*Indirect comparisons of proportional effects of different antiplatelet regimens on deep venous thrombosis detected by systematic fibrinogen scans or venography, or both. Symbols and conventions as in figures 1 and 6*

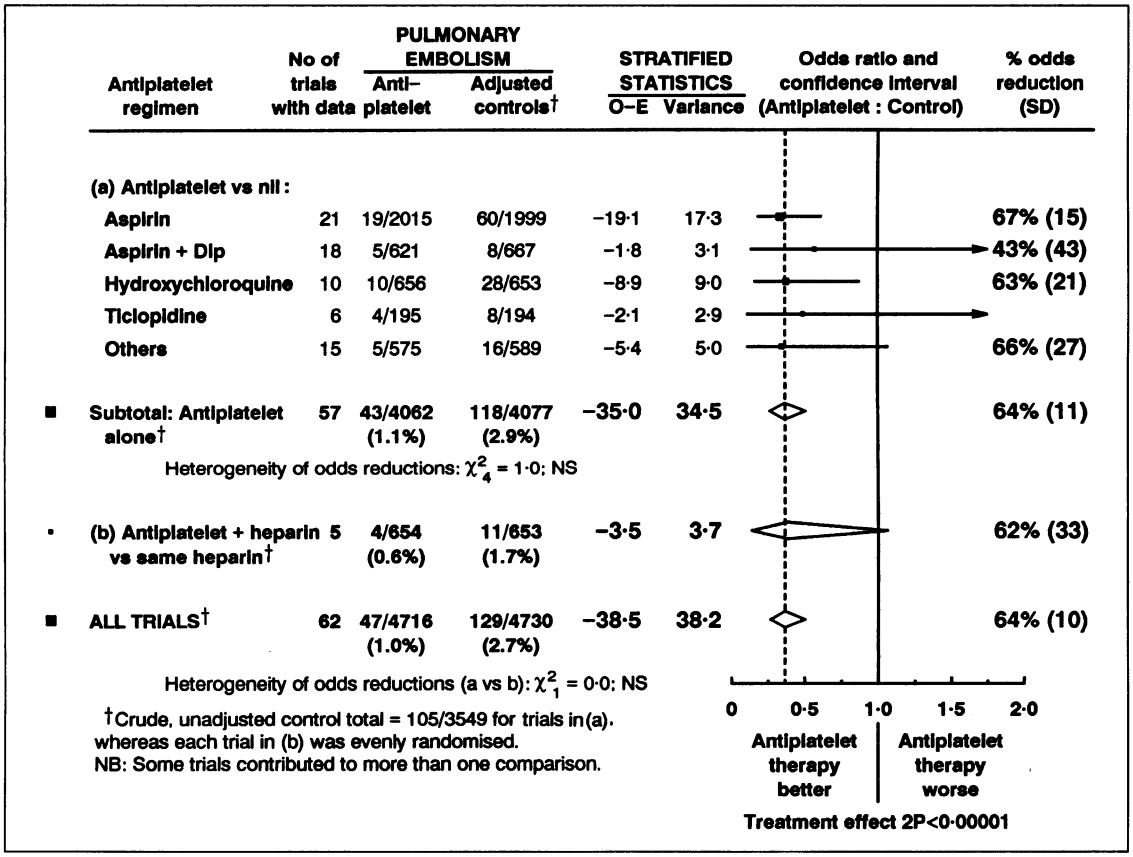

FIG 8—*Indirect comparisons of proportional effects of different antiplatelet regimens on pulmonary embolism in trials that sought venous thrombosis systematically. Symbols and conventions as in figures 1 and 6*

concomitant anticoagulant therapy) and antiplatelet therapy plus heparin versus the same heparin regimen. As before, the chief problem is that the number of statistical comparisons is so large that some results are likely to have been substantially distorted by the play of chance. For deep venous thrombosis assessed by fibrinogen scanning or venography, or both (fig 7), the most extensively tested regimens were aspirin, aspirin plus dipyridamole, hydroxychloroquine, and ticlopidine. All except ticlopidine were significantly protective. The most promising were aspirin plus dipyridamole and hydroxychloroquine, which accounted for the statistical significance of the heterogeneity between the apparent effects of these regimens on deep venous thrombosis—though it is difficult to know how far to trust such indirect comparisons between the sizes of the apparent benefits in different trials. For pulmonary embolism (fig 8) the greatest amount of evidence related to aspirin and to hydroxychloroquine, each of which appeared to reduce pulmonary embolism by about two thirds, but there was no good evidence of heterogeneity between the effects of the different antiplatelet regimens.

Most trials assessed the thromboprophylactic efficacy of antiplatelet therapy in the absence of subcutaneous heparin, so that information on adding antiplatelet therapy to heparin was limited (figs 7 and 8). For preventing pulmonary embolism, however, it did appear that the effects of antiplatelet therapy might be, at least in part, additive to those of heparin (four (0·6%) patients with pulmonary embolism among 654 patients allocated antiplatelet plus heparin versus 11 (1·7%) among 653 allocated the same heparin regimen alone; $2P < 0·05$; fig 8).

EFFECTS OF THERAPY ON SURGICAL BLEEDING

Fatal bleeds were rare and there was no significant difference between the treatment groups (two (0·05%) *v* nil; fig 5). The non-fatal major haemorrhagic complication for which information was available from most surgical trials was need for transfusion, with a marginally significant trend towards more such "major" bleeds among treatment allocated patients (0·7% antiplatelet therapy *v* 0·4% control; one sided P (1P) = 0·04), equivalent to three (SD 2) additional patients being transfused per 1000 treated (table III). Information on other complications (reoperations, wound haematomas, or infections due to bleeding) was also quite commonly available from these surgical trials, and there was a definite excess with antiplatelet therapy (7·8% *v* 5·6%; 1P = 0·003), equivalent to a complication rate of about 22 (SD 9) per 1000 patients. Similar increases in this complication were seen in general surgery and in orthopaedic surgery and when the analyses were confined to placebo controlled studies.

Discussion

It is sometimes supposed that the randomised trials of antiplatelet prophylaxis have shown this treatment to have little or no effect on venous thrombosis or pulmonary embolism.[3-8] But this systematic overview of the findings among about 9000 randomised patients brings together far more evidence than was previously conveniently available and shows conclusively that antiplatelet therapy (usually given for only about one to three weeks) substantially reduces both the incidence of deep venous thrombosis and, particularly, the incidence of pulmonary embolism in a wide range of surgical patients. The limited evidence so far available about antiplatelet therapy in medical patients who are at high risk of deep venous thrombosis is also encouraging. When some allowance is made for the imperfect compliance with allocated treatment that inevitably happens in clinical trials (see discussion in part I) it seems that a few weeks of antiplatelet therapy can almost halve the odds of suffering a deep venous thrombosis and can reduce pulmonary embolism by more than half.

TABLE III—*Reported bleeding complications in trials of antiplatelet thromboprophylaxis among surgical patients that sought deep venous thrombosis systematically*

Complication reported	No of trials with data	Antiplatelet group	Adjusted controls	Absolute excess per 1000 (SD)	Statistical significance (1P)
Fatal bleed	53	2/4441 (0·05%)	0/4450 (0%)	—	NS
Non-fatal "major" bleed (that is, need for transfusion)	45	28/3798 (0·7%)	15/3808 (0·4%)	3 (2)	=0·04
Reoperation, haematoma, or infection due to bleed	25	177/2269 (7·8%)	129/2306 (5·6%)	22 (9)	=0·003

RELIABILITY OF MAIN FINDINGS

Deep venous thromboses are difficult to assess reliably, but although such difficulties might lead to false negative trial results, they should not lead to false positive trial results. Nor can the reductions in deep venous thrombosis observed with antiplatelet therapy be ascribed to any treatment related biases in the ascertainment of thrombus by fibrinogen scanning[88] (see above). In confirmation of this, the highly significant ($2P < 0·00001$) reduction in deep venous thrombosis associated with antiplatelet therapy that was observed separately in general surgery, in traumatic orthopaedic surgery, and in elective orthopaedic surgery (as well as among the few high risk medical patients in thromboprophylaxis trials) remained highly significant when the analyses were confined to placebo controlled trials, to venographically confirmed thromboses, or even to placebo controlled trials that used systematic venography to detect thrombosis. Finally, the reduction was seen not only in distal vein thromboses but also in proximal (femoral or iliac) vein thromboses, which are particularly liable to embolise.

Pulmonary emboli are also difficult to assess reliably, but again the large reduction in pulmonary embolism in those trials that sought venous thromboses systematically (47 (1·0%) antiplatelet therapy *v* 129 (2·7%) control) cannot plausibly be ascribed to biases. The 95% confidence interval for this reduction of about two thirds in pulmonary embolism ranges from a reduction of about one half to a reduction of about three quarters. A similar sized reduction in the placebo controlled trials confirms that the subjective nature of the determination of pulmonary embolism is unlikely to have introduced any material bias into this assessment of antiplatelet prophylaxis.

EFFECTS ON ALL CAUSE MORTALITY

The most important hazard is fatal pulmonary embolism, and for this also the effects of antiplatelet therapy were highly significantly beneficial (11 (0·2%) deaths attributed to pulmonary embolism among the 4441 surgical patients allocated antiplatelet therapy versus an adjusted total of 39 (0·9%) among 4450 controls; $2P = 0·0001$). One important aim of prophylaxis is to reduce total mortality. But the statistical power to detect this directly is low, even in this overview of all the antiplatelet trials (table I), because total mortality is subject to uninformative chance fluctuations in other causes of death that are not likely to be much influenced by antiplatelet therapy. Thus a direct assessment of the effect of treatment on total mortality by a crude analysis of "all deaths" (which ignores what is known of their causes) may, paradoxically, be less reliably informative about the effects of treatment on total mortality than an indirect assessment would be that is based on separate analyses of the deaths attributed to pulmonary embolism, to

haemorrhage, and to an aggregate of all other causes. So, although the reduction in all deaths was only non-significantly favourable, the reduction in deaths ascribed to the aggregate of pulmonary embolism or haemorrhage, or both, was highly significant and not associated with any significant difference in deaths from other causes.

SIMILAR PROPORTIONAL REDUCTIONS IN PULMONARY EMBOLISM IMPLY GREATER BENEFIT FOR THOSE AT HIGHER RISK

A further limitation of basing inference directly on a crude analysis of the aggregate of all deaths would be that the proportion by which fatal pulmonary embolism is reduced is likely to be more widely generalisable to different patient populations than is the proportion by which total mortality is reduced (as there may be wide differences between different types of patient in the ratio between deaths due to pulmonary embolism and deaths due to other causes). The proportional reductions in overall (fatal or non-fatal) pulmonary embolism appeared to be roughly similar in different types of patient (fig 3). If the same is true for fatal pulmonary embolism, then the absolute mortality reduction should be greatest in patients in whom the chances of a fatal pulmonary embolism are highest. For example, a reduction by two thirds in the number of deaths from pulmonary embolism would produce a large absolute reduction in total mortality among those at high risk of such emboli (for example, elderly immobilised patients, or those having lengthy or orthopaedic surgery) but would have much less effect among patients at low risk of embolism (for example, children or young adults).

CHOICE OF ANTIPLATELET REGIMEN

Comparisons between different antiplatelet regimens may be based on several factors, including efficacy, ease of use, severity of side effects, and cost. Aspirin is the most widely tested antiplatelet regimen, with the best evidence of substantial protective effects against pulmonary embolism and other major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death; see part I) and is convenient, familiar, and inexpensive. Further research is, however, needed to determine whether a combination of aspirin plus dipyridamole really is more effective than aspirin alone in preventing deep venous thrombosis. The directly randomised evidence on deep venous thrombosis seems promising and may reflect some real biological differences in effect.[89-91] But the large number of comparisons between different regimens that have been made in the different parts of this overview mean that the nominal statistical significance of this particular one may yet be found to have been largely or wholly due to the play of chance. Moreover, if attention is directed to pulmonary embolism or to other clinically important vascular events, then the directly randomised comparisons do not support the hypothesis that adding dipyridamole might materially improve the effects of aspirin alone (table II).

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

Fatal pulmonary embolism may be rarer now than when many of the trials reviewed were conducted, but it still causes a few deaths per 1000 operations in middle aged and older people in Europe and North America.[2-4 92] A few weeks of antiplatelet therapy appeared to prevent about two thirds (or, given the statistical uncertainties, at least one half) of the pulmonary emboli occurring after many types of surgery. The reduction in deaths attributed to pulmonary embolism in these trials was highly significant and not associated with any significant increase in deaths attributed to other causes. Such treatment appeared to reduce the risk of pulmonary embolism and deep venous thrombosis by a similar proportion among patients having general surgery, traumatic orthopaedic surgery, or elective orthopaedic surgery (as well as among high risk medical patients).

Clinical implications

- Prolonged general and orthopaedic surgery (as well as other periods of limited mobility) are associated with increased risks of venous thromboembolism
- A few weeks of antiplatelet therapy roughly halved the risk both of deep venous thrombosis and of pulmonary embolism in a wide range of surgical patients (and the limited evidence in immobilised medical patients was also encouraging)
- The absolute benefits appeared to be greater for those at higher risk (for example, those undergoing orthopaedic surgery)
- Antiplatelet therapy can be conveniently continued after discharge from hospital (in contrast with many other forms of prophylaxis) for as long as the risk of thromboembolism is still substantial
- Antiplatelet therapy—either alone or, for greater effect, in addition to other proved forms of thromboprophylaxis—should be considered for patients at high risk of thromboembolism

No consistent measures of bleeding complications were available, but the overview of the information that has been supplied suggests that the risks of significant bleeding were small. Hence antiplatelet therapy appears to offer a safe and effective means of thromboprophylaxis in patients having many types of surgery, as well as in other high risk groups of patients. Moreover, it would be practicable to continue it after discharge from hospital (in contrast with many other forms of prophylaxis) for as long as the risk of thromboembolism is still substantial.[79 80] This does not imply that some other proved method of thromboprophylaxis (for example, low dose subcutaneous heparin[10]) could not be used in addition to antiplatelet therapy. But other methods alone may not suffice, since, at least for pulmonary embolism, antiplatelet therapy appears to confer additional protective effects even when low dose heparin is also being used, though the data are sparse.

Treatment recommendations depend on a wide variety of considerations, of which trial results are only one part. Trial results—or, better, statistically definite overviews of them—provide information, not instructions, to those concerned with treatment. But when individual trials or overviews do—as for the effects on pulmonary embolism of antiplatelet therapy (and of anticoagulant therapy[10])—produce very definite results, then surgeons and physicians with high risk patients should at least make themselves familiar with those answers and with the reliability of the methods that produced them. This should lead to much larger trials, which could determine more reliably the types of patient in whom the major benefits outweigh the major risks, or which could assess the relative merits of antiplatelet, anticoagulant, and combination therapy. Indeed, one such trial (the pulmonary embolism prevention trial) is already in progress. It should also confirm, particularly among orthopaedic surgeons and general surgeons, the importance of thromboprophylaxis among many types of patient who would otherwise be at substantial risk of a disabling or fatal pulmonary embolism.

Appendix 1

INDIVIDUAL RESULTS OF UNCONFOUNDED RANDOMISED COMPARISONS OF ANTIPLATELET THERAPY WITH CONTROL (A *v* C) FOR THROMBOPROPHYLAXIS IN SURGICAL AND HIGH RISK MEDICAL PATIENTS

Trial name	Reference No	Regimen†	Control and follow up methods‡	Weeks of treatment	No of patients§		Deep venous thrombosis				Pulmonary embolism				Non-pulmonary embolism deaths¶		Reoperation, wound haematoma/ infection		Major bleed	
							Any‖		Proximal		Non-fatal		Fatal							
					A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
General surgery																				
MRC	13	A600	P F	1	153	150	42	33	—	—	0	0	0	0	0	0	—	—	—	—
Parodi-I	14, 15	Dip, A1000+Dip	O F+V	1	40	22×2	6	9	—	—	0	0	0	0	0	0	0	0	—	—
Parodi-II	14, 15	A1500, Dip, A+Dip	O F	1	91	35×3	16	13	1	2	0	0	0	0	0	0	0	0	0	0
Loew DVT	16	A600	P C+V	2	702	679	(5	11)	—	—	2	10	2	7	2	2	80	70	0	0
Zekert-III	17	A1500, A1300+Dip, A1000+Dip	O F	2	135	46×3	54	16	—	—	4	0	0	0	7	1	—	—	3	0
Clagett	18	A1300	O F+V	1	56	49	9	11	—	—	0	0	0	0	0	0	—	—	0	0
Australian-I	19	A1000+Dip	O F	1	75	75	13	35	—	—	—	—	—	—	—	—	—	—	—	—
Australian-II	20	A1000+Dip	O F	1	85	75	12	24	—	—	1	1	0	0	0	0	—	—	0	0
Encke-IA	21	A990, A+Dip	P F	2	21	9×2	12	4	—	—	0	0	0	0	0	0	—	—	0	0
Encke-IB	21	A1500, A990+Dip	P F	2	62	34×2	12	13	—	—	0	0	0	0	0	0	—	—	0	0
Toulouse-I	22	A990+Dip	O F	1	38	66	3	14	—	—	0	0	0	0	0	0	0	0	0	0
Erfurt-A	23, 24	A1500	P D/F+V	2	357	357	(9	32)	—	—	0	0	0	3	0	0	—	—	3	0
Zekert-V	25	A1500+Hep *v* Hep	P F+V	2	50	49	12	16	5	5	0	1	0	0	0	0	1	2	4	1
Vinazzer-I	26	A1500+Hep *v* Hep	P D+V	1	402	404	(1	9)	—	—	0	2	0	1	17	7	41	13	1	0
Vinazzer-II	27	A1000+Hep *v* Hep	P F	1	62	62	5	11	0	5	0	0	0	2	0	1	0	0	0	0
Zekert-VI	28, 29	A1500	O F	2	50	50	16	12	3	0	0	1	0	0	0	0	0	0	0	0
Harjola-DVT	30	A1500, Dip, A+Dip	O C+V	2	300	100×3	(6	5)	—	—	0	0	0	2	0	0	—	—	0	0
Lasierra	31	Ticlopidine	P sysV	2	40	40	8	12	2	4	0	0	0	0	0	0	—	—	—	—
Athens	32	Sp	P F	1	48	48	7	14	—	—	0	2	0	0	0	0	—	—	0	0
Turpie	33	Suloctidil	P F	1	68	68	17	12	2	3	0	0	0	0	4	4	—	—	4	3
Veth	34	Sp+Hep *v* Hep	O F	1	120	118	20	14	—	—	4	4	0	0	0	0	0	0	0	0
Carter-IA	35	Hydroxy	P C	1	284	281	(0	25)	—	—	2	16	0	0	0	0	—	—	—	—
Carter-IB	35	Hydroxy	P sysV	1	26	26	0	6	—	—	—	—	0	0	0	0	—	—	—	—
Carter-II	36	Hydroxy	P F+V	2	107	97	5	17	0	1	0	0	0	0	0	0	—	—	0	0
Walker	37	Ticlopidine	P F	2	31	33	7	9	—	—	—	—	0	0	0	0	—	—	—	—
Weiss	38	A990+Dip	O F	2	30	36	1	11	—	—	0	1	0	0	0	0	—	—	0	0
New York	39	Hydroxy	P F	1	46	44	1	6	—	—	—	—	—	—	—	—	—	—	—	—
Vermont	40	Hydroxy	P Pl	2	50	58	(1	5)	—	—	1	1	0	0	0	0	0	0	0	0
Traumatic orthopaedic surgery																				
Wood	41	RA233, A600+RA233	P F	2	21	9×2	20	6	16	5	0	0	1	1	2	1	0	0	0	0
Zekert-I	42-44	A1500	P F+V	2	138	140	7	17	—	—	2	6	1	8	5	6	16	11	0	2
Morris-A	45	Dip	O F	1	24	24	15	16	—	—	—	—	0	0	0	0	0	0	0	0
Morris-B	45	A900+Dip	O F	1	32	32	20	21	—	—	0	0	0	0	0	0	0	0	0	0
Morris-C	45	Flurbiprofen	O F	1	20	20	13	12	—	—	0	0	0	0	0	0	0	0	0	0
Powers	46	A1300	P F+V	3	66	63	27	29	7	19	0	2	1	0	2	1	—	—	1	1
Danish-A	47	Hydroxy	P F	3	48	50	24	33	—	—	1	3	0	2	0	0	—	—	0	0
Danish-B	47	Hydroxy	P F	3	27	28	7	18	—	—	1	0	0	0	0	0	—	—	0	0
Massachusetts-I	48	A1200, A+Hydroxy	O C/Pl+V	3	50	25×2	(13	15)	—	—	0	2	1	0	3	1	8	3	7	3
Encke-II	21	A1500, A990+Dip	P F	2	34	25	14	8	—	—	1	1	0	1	2	1	—	—	0	0
Erfurt-B	23, 24	A1500	P F+V	2	44	44	16	20	—	—	0	0	5	5	0	0	—	—	0	0
Elective orthopaedic surgery																				
Stockholm-I	49	A2000	P C	2	26	25	(7	4)	—	—	0	0	0	0	0	0	—	—	0	0
Lyon-I	50	A1500+Dip	O F	2	20	20	10	8	—	—	0	0	0	0	0	0	—	—	0	0
Massachusetts-II	51	Hydroxy	P C/Pl+V	3	51	51	(1	8)	—	—	0	2	0	2	0	0	7	9	2	2
Pasteyer	52	A1000+Hep *v* Hep	O sys V	2	20	20	4	4	0	1	0	1	0	0	0	0	1	2	1	0
Harris-I	53	A1200	P F	1	58	59	11	23	5	14	0	1	0	0	0	0	3	1	0	0
McKenna-I	54	A975, A3900	P F+V	2	24	12×2	8	9	2	3	3	4	0	0	0	0	—	—	1	0
Sautter	55	A900+Sp	P F+V	3	68	77	33	52	13	29	2	5	0	0	0	0	4	5	0	0
Cooke	56	Hydroxy	P T+V	2	25	25	(10	12)	—	—	5	2	0	0	0	0	1	1	0	0
Rocha	57	A250, A1000	O F+V	1	60	30×2	3	11	—	—	0	1	0	0	0	0	2	1	0	0
McKenna-II	58	Ticlopidine	P F+V	2	29	29	14	16	—	—	2	3	0	0	0	0	6	0	0	0
McBride	59	A1800+Dip	P F	1	21	22	8	8	—	—	0	0	0	0	0	0	—	—	—	—
Hume-A	60, 61	Hydroxy	P F+V	2	20	20	10	10	—	—	—	—	0	0	0	0	—	—	0	0
Lyon-II	62	Ticlopidine	P F	3	20	20	8	13	—	—	1	0	0	0	0	0	6	5	0	0
Gardecki	63, 64	Ticlopidine	P F+V	2	48	46	36	39	14	12	1	3	0	0	0	0	1	2	—	—
Stockholm-II	65	Hydroxy	P F	2	18	17	12	11	—	—	0	0	0	0	0	0	—	—	0	0
Hamburg	66	A+Dip, A1000	P F	3	21	11×2	3	4	—	—	0	0	0	0	0	0	—	—	1	0
High risk medical patients																				
Chicago	68	A600+Dip	O F+V	4	13	15	3	6	0	0	0	0	0	0	0	0	—	—	—	—
Denver-I	69	Sp	P C+V	13	14	14	(0	3)	—	—	0	0	0	0	0	1	—	—	—	—
Denver-II	70	A1200+Dip	P sysV	78	19	19	1	7	1	7	0	1	0	0	0	0	—	—	—	—
Toulouse-II	71	A990+Dip	P F	1	40	40	6	14	—	—	1	0	0	0	7	5	—	—	—	—
McKenna-III	72	Ticlopidine	P F+V	2	27	26	10	5	—	—	0	2	0	0	0	2	—	—	—	—
Den Ottolander	73	A1500+RA233	P F	3	14	14	3	7	—	—	—	—	2	2	1	1	—	—	0	0
GRAND	74	GR32191B	P F	3	63	64	6	7	—	—	0	0	0	0	3	5	—	—	—	—
Jones	75	Dazoxiben	P F	4	60	60	8	13	—	—	—	—	0	1	10	10	—	—	0	1
Frankfurt	76	A+Dip, A1320	P F	2	25	14×2	2	1	—	—	0	0	0	1	1	0	—	—	0	0

—Data not available.

†A=Aspirin (expressed with daily dosage in mg, unless same in both arms). Dip=Dipyridamole. Hep=Heparin. Sp=Sulphinpyrazone. Hydroxy=Hydroxychloroquine. RA233 and GR32191B are unmarketed antiplatelet agents.

‡P=Placebo. O=Open randomised control. F=Systematic radiolabelled fibrinogen uptake scanning. +V=Confirmatory venography. C=Clinical examination. D=Doppler ultrasonography. sysV=Systematic venography. Pl=Plethysmography. T=Thermography.

§"×2," "×3" denote control groups counted twice, thrice in adjusted totals to balance larger treatment groups.

‖Figures within parentheses are numbers of deep venous thromboses detected in trials using methods other than systematic radiolabelled fibrinogen uptake scanning (with or without venography) or systematic venography.

¶Includes fatal bleeds and other deaths. Overall two deaths[73 75] were attributed to bleeding among antiplatelet allocated patients versus two among controls.[72 75]

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Appendix 2

INDIVIDUAL RESULTS OF UNCONFOUNDED RANDOMISED COMPARISONS OF ONE ANTIPLATELET REGIMEN WITH ANOTHER (A1 *v* A2) FOR THROMBOPROPHYLAXIS IN SURGICAL AND HIGH RISK MEDICAL PATIENTS

Trial name	Reference No	Regimen†	Control and follow up methods‡	Weeks of treatment	No of patients§		Deep venous thrombosis				Pulmonary embolism				Non-pulmonary embolism death		Reoperation, wound haematoma/ infection		Major bleed	
							Any‖		Proximal		Non-fatal		Fatal							
					A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2	A1	A2
General surgery																				
Parodi-I	14,15	A1000+Dip *v* Dip	O F+V	1	21	19	2	4	—	—	0	0	0	0	0	0	0	0	—	—
Parodi-II	14,15	A+Dip *v* A1500	O F	1	31	30	3	7	0	0	0	0	0	0	0	0	0	0	0	0
Parodi-II	14,15	Dip *v* A1500	O F	1	30	30	6	7	1	0	0	0	0	0	0	0	0	0	0	0
Parodi-II	14,15	A1500+Dip *v* Dip	O F	1	31	30	3	6	0	1	0	0	0	0	0	0	0	0	0	0
Zekert-II	17	A1000+Dip *v* Dip	O F	2	17	19	6	8	—	—	0	1	0	0	0	0	—	—	—	—
Zekert-II	17	Dip *v* A1500	O F	2	19	15	8	5	—	—	1	0	0	0	0	0	—	—	—	—
Zekert-II	17	A1000+Dip *v* A1500	O F	2	17	15	6	5	—	—	0	0	0	0	0	0	—	—	—	—
Zekert-III	17	A1000+Dip, A1300+Dip *v* A1500	O F	2	89	46×2	33	21	—	—	3	1	0	0	1	6	—	—	1	2
Encke-IA	21	A+Dip *v* A990	P F	2	12	9	6	6	—	—	0	0	0	0	0	0	—	—	0	0
Encke-IB	21	A990+Dip *v* A1500	P F	2	30	32	3	9	—	—	0	0	0	0	0	0	—	—	0	0
Harjola DVT	30	A+Dip *v* A1500	O C+V	2	100	100	(0	4)	—	—	0	0	0	0	0	0	—	—	0	0
Harjola DVT	30	A1500+Dip *v* Dip	O C+V	2	100	100	(0	2)	—	—	0	0	0	0	0	0	—	—	0	0
Harjola DVT	30	Dip *v* A1500	O C+V	2	100	100	(2	4)	—	—	0	0	0	0	0	0	—	—	0	0
Traumatic orthopaedic surgery																				
Wood	41	A600+RA233 *v* RA233	P F	2	9	12	9	11	7	9	0	0	0	1	2	0	0	0	0	0
Massachusetts-I	48	A+Hydroxy *v* A1200	O C/Pl+V	3	26	24	(7	6)	—	—	0	0	0	1	2	1	7	1	6	1
Encke-II	21	A990+Dip *v* A1500	P F	2	18	16	6	8	—	—	0	1	0	0	0	2	—	—	0	0
Elective orthopaedic surgery																				
McKenna-I	54	A975 *v* A3900	P F+V	2	11	13	7	1	2	0	2	1	0	0	0	0	—	—	1	0
Rocha	57	A250 *v* A1000	O F+V	1	30	30	1	2	—	—	0	0	0	0	0	0	1	1	0	0
Hume-B	60,61	A+Hydroxy *v* A1300	P F+V	2	20	21	5	7	—	—	—	—	0	0	0	0	—	—	—	—
Hamburg	66	A+Dip *v* A1000	P F	3	11	10	1	2	—	—	0	0	0	0	0	0	—	—	1	0
Harris-II	67	A300 *v* A1200	O sysV	<2	50	50	26	29	5	16	2	0	0	0	0	0	—	—	—	—
High risk medical patients																				
Frankfurt	76	A+Dip *v* A1320	P F	2	11	14	0	2	—	—	0	0	0	0	0	1	—	—	0	0
Hart	77	A+Dip *v* A1500	O F	<2	44	46	5	16	—	—	—	—	0	0	0	0	—	—	—	—
Capildeo	78	A+Dip *v* A900	P T+V	2	88	95	(21	15)	—	—	0	0	1	0	8	5	—	—	—	—

—Data not available.
†A=Aspirin (expressed with daily dosage in mg, unless same in both arms). Dip=Dipyridamole. Hydroxy=Hydroxychloroquine. RA233 is unmarketed antiplatelet agent.
‡O=Open randomised control. P=Placebo. F=Systematic radiolabelled fibrinogen uptake scanning. +V=Confirmatory venography. C=Clinical examination. Pl=Plethysmography. sysV=Systematic venography. T=Thermography.
§"×2" denotes control group counted twice in adjusted total to balance larger treatment group.
‖Figures within parentheses are numbers of deep venous thromboses detected in trials using methods other than systematic radiolabelled fibrinogen uptake scanning (with or without venography) or systematic venography.

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Severe anaphylactic reaction to latex rubber surgical gloves

P I Mansell, J P D Reckless, C R Lovell

Royal United Hospital, Bath BA1 3NG
P I Mansell, *senior medical registrar*
J P D Reckless, *consultant physician*
C R Lovell, *consultant dermatologist*

Correspondence to:
Dr P Mansell, c/o Dr Leatherdale's secretary, Royal South Hants Hospital, Southampton SO9 4PE.

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Immediate hypersensitivity to rubber is fairly common among people regularly exposed to rubber, although severe anaphylactic reactions are rare.[1 2] We report a severe anaphylactic reaction in a woman who may have been sensitised to rubber during multiple operations and vaginal examinations.

Case report

A 31 year old woman became ill on her way home from a hospital consultation. Her face and eyelids swelled, her throat felt tight, and she became short of breath with wheezing. Her general practitioner arrived to find her moribund; diagnosed anaphylaxis; and injected adrenaline, chlorpheniramine, and hydrocortisone. She survived a respiratory arrest during transfer to hospital.

The woman's medical history included delayed hypersensitivity reactions to nickel and several operations (including appendicectomy, herniorrhaphy, right salpingo-oophorectomy, two laparoscopies, and four caesarean sections). During a consultation about an abscess at the site of a stitch the woman's gynaecologist had examined her vaginally while wearing a latex rubber glove; the anaphylactic reaction occurred about 10 minutes later. In retrospect, she recalled a less severe episode of facial swelling and wheezing after blowing up some balloons. Immediate hypersensitivity to latex rubber was thought to have caused her anaphylactic reaction.

The woman recovered fully within 24 hours and was discharged from hospital with syringes preloaded with adrenaline (0·5 ml 1/1000) for intramuscular injection and 240 mg of terfenadine to take orally at the onset of any attack. A blood sample taken 36 hours after the anaphylactic reaction showed normal C3 and C4 concentrations and a C1 esterase inhibitor concentration of 0·12 g/l (reference range 0·15-0·35 g/l), which excluded idiopathic angio-oedema.

The patient was subsequently noted to be dermatographic and had a positive hypersensitivity reaction 10 minutes after a prick test with a 1 cm square piece of a latex rubber glove but no reaction when a control polythene glove was used. Prick testing with natural rubber latex showed a 5 mm weal and 15 mm flare; no reactions were obtained in six control subjects. A resuscitation trolley, a syringe preloaded with adrenaline, and a plastic airway were close by during these tests. Patch tests with various rubber chemicals gave negative results, though those with nickel and cobalt gave positive results.

Four months later the woman developed wheezing and shortness of breath 30 minutes after her son directed the flow of air from a deflating rubber "whoopee" cushion (a joke cushion) at her face. She injected adrenaline, and the resulting reaction was less severe than the previous reaction, but admission to hospital was still required.

Comment

Immediate hypersensitivity is fairly common among people regularly exposed to rubber. Nine of 145 theatre staff in one Finnish hospital had local contact urticaria caused by wearing latex rubber surgical gloves, and similar allergic reactions occur in people who regularly use rubber cleaning gloves.[1]